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14. ABSTRACT

The objectives of this project were to develop computer based models of soft tissues that could eventually be integrated into virtual reality-based surgical simulators. To that end, we have developed a number of computer algorithms that span the scales from the microstructural to the phenomenological, and from 1-D to 3-D. For the 1-D case, we have developed a model of fractional order viscoelasticity. For the 3-D case, we have developed an invariant-based formulation of dispersed isotropy and implemented it in a model of blood vessel. Although the later employs as statistical measure of fiber dispersion, both a essentially phenomenological models. To implement tissue microstructure, we developed a micromechanical model based on the General Method of Cells. Through this model, we were able to model fiber-matrix interactions explicitly. These models are currently being validated and implemented into larger organ simulations.

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Introduction

The objectives of this 3-year project were to formulate high fidelity computational models for soft biological tissues that can eventually be implemented within existing software for use in telemedicine and surgical simulation. We proposed to implement quasi-linear viscoelastic theory (QLV) in 3D, develop fractional-order viscoelasticity (FOV) to a higher level, and implement more sophisticated 3-D models into simulations of soft tissue behavior. As a laboratory with long experience in experimental work and validation, we also proposed to perform bench studies and tissue loading experiments so that these models could be properly validated.

Body

Our general approach can categorized into: (i) theoretical development, (ii) algorithmic development/coding, (iii) code validation through analytical solutions when these exist, (iv) theory/code validation through comparison with experimental data and, (v) simulating a number of simple but realistic surgical processes. In this report, the individual accomplishments will be reported in separate sections.

(a) Improved parameter estimation methods and novel experimental techniques

A new parameter estimation method for QLV that is less sensitive to imperfections in the experimental data has been developed and published [1]. The method is robust, insensitive to the loading history of the test specimen and handles noise in the position channel quite well. Although this is a one-dimensional approach, it is remarkably predictive of the time-varying, one dimensional response of elongated structures, such as ligaments, tendons, and strips of tissue. This approach would thus be useful for modeling surgery of tissue strips with the appropriate geometry.

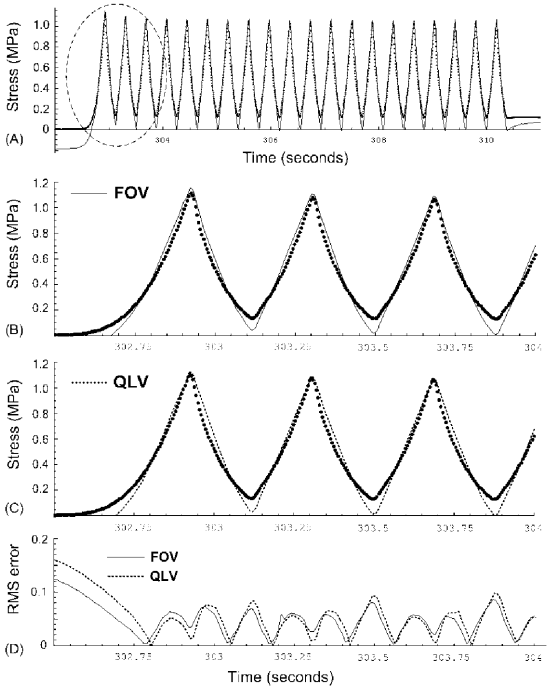

Figure 1: Plots of the cyclic response data and model predictions for a typical specimen for (a) all 20 cycles, and expanded to the first 3 cycles (b & c). Also shown is the pointwise RMS error for both methods (d).

(b) New theoretical and numerical developments for fractional-order viscoelasticity (FOV)

Most previous studies of soft tissue viscoelasticity have used Boltzmann's general theory of viscoelasticity, extended to include nonlinear elastic behavior and a continuous box-spectrum relaxation response (Fung's well-known quasilinear viscoelasticity theory, QLV). We have introduce an

[1] Doehring T.C., Carew E.O., Vesely I. The effect of strain rate on the viscoelastic response of aortic valve tissue: a direct-fit approach. Ann.Biomed.Eng. 32(2):223-32, 2004.

alternative: the fractional order viscoelasticity (FOV) theory, which uses a fractional integral for the relaxation response. FOV has some appealing characteristics, such as more flexible control over the early relaxation behavior. FOV also implies a hierarchical (fractal-like) structure, which is relevant to connective tissues[2]. The theoretical work regarding the implementation of FOV has been completed by our German colleague, Dr. Kai Diethelm and two publications have resulted [3,4]. We validated the fidelity of this method by comparing a predicted viscoelastic response of a modeled experiment with the real acquired data and found errors typically below 2% (see Fig. 1). Overall, FOV is only slightly better than QLV in predicting long term stress relaxation and cyclic loading, but shows promise because of its hierarchical nature that is more representative of the internal complexity of biological tissues.

(c) Validation of the Anisotropic Hyperviscoelastic (ANHVE) model with soft biological tissues

Early in the program, we contracted Dr. Saleeb at the University of Akron to implement his ANHVE model (previously referred to as the LSVEA formulation) to soft biological tissues. This model, by definition, is a phenomenological model, in that the various parameters estimated for the multi-mechanism model of the material in question, do not have any physical representation. We nevertheless pushed ahead with this approach because it is computationally expedient. Validation of the ANHVE model involved parameter estimation from biaxial (2D) experiments and subsequent simulations of independent uniaxial, biaxial (planar) and inflation (nonplanar) tests. The response predicted by the numerical approach was reasonable (see Fig. 2) but refinement is needed. Tuning of the model for more complex structures became difficult, so we thus opted to develop our own model, incorporating features of the tissue that are more directly observable – the fiber distribution population – as shown in the next section.

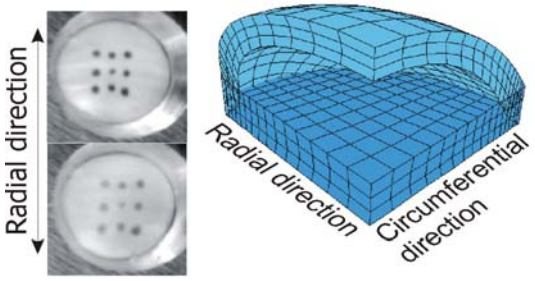

Figure 2: Image (left) of a presurized segment of aortic valve tissue showing how the markers on the surface more apart in response to the distension of the membrane. An FEA representation of the same experiment (right) showing the anisotripic deformation of the tissue segment, being different in the two principle fiber directions.

(d) Invariant theory for dispersed transverse isotropy.

The past few years have seen an increased interest in nonlinear continuum mechanics as a framework for describing the mechanical behavior of soft biological tissues. The mathematics in this field are now well-established and thus provide a foundation for thermodynamically-consistent constitutive equations. These equations are readily handled by the theory of invariants, and incorporate finite deformations, geometric and material nonlinearities and tissue anisotropy. Powerful computers and well-developed computational techniques now make

[2] Doehring T.C., Freed A.H., Carew E.O., Vesely I., Fractional order viscoelasticity of the aortic valve: An alternative to QLV. J. Biomech. Eng. 127(4):700-8, 2005.
[3] Diethelm K., Ford N.J., Freed A.D., Luchko Yu., Algorithms for the fractional calculus: A selection of numerical methods. Computer Methods in Applied Mechanics and Engineering, 194:734-773, 2005.
[4] Diethelm K., Weilbeer M., A numerical approach for Joulin's model of appoint source initiated flame. Fractional Calculus and Applied Analysis, (7):2, 191-212, 2004.

simulations of tissue-level mechanics feasible. Interactions between crossing fiber populations have been implicated in generating the complex biaxial material properties of most biological tissues. For example, under certain combinations of biaxial tension, the material can shrink in one principle direction of applied stress Our recently developed a constitutive equation for soft-tissues based on a new invariant theory for dispersed transverse isotropy[5]. The current model replaces a numerically evaluated integral with a single analytic scalar, and is thus computationally expedient, increasing the speed of our simulations three fold.

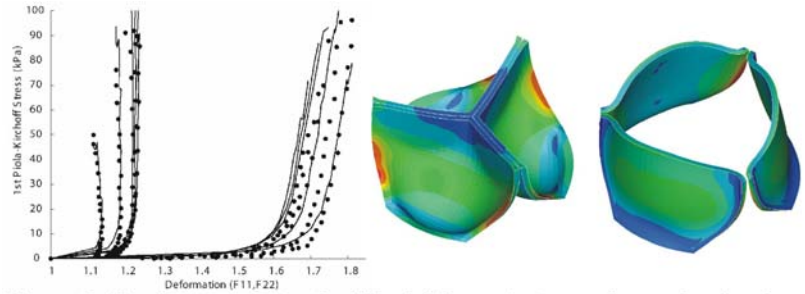

Figure 3: Simulations of standard biaxial tissue tests produce a family of stress/strain curves that correspond closely to the raw data (left). Finite element simulations based on the new model demonstrate physiologic patterns of stress and leaflet configuration in open and closed position.

In our first validation, we made use of our long standing expertise in heart valve biomechancis, and simulated the opening and closing behavior of an artificial heart valve. The first part of the simulation involved first fitting the model to experimental data of a series of biaxial tensile tests of the leaflet material. The fit of our model to these experimental data (see Fig. 3) demonstrates that our model can simulate both the non-linear stress/strain behavior of this tissue, as well as the lateral contraction that occurs under certain combinations of biaxial loading. The resulted simulation of making use of this material model showed very good agreement to know behavior of heart valve tissues.

(e) Micromechanical model

To obtain the greatest fidelity of a model to the real material, one must take into account the internal microstructure. To that end, we have been working with Drs. Pindera and Aboudi, from the University of Virginia to complete the development of a high-fidelity micromechanical model. This model uses the principle of Generalized Method of Cells (GMC) and can predict both the macro-level response and the micro-level stress and deformation fields in the individual material phases. GMC assumes that a region of material space consists of a periodic array of cells with identical microstructure and material properties. A "homogenization technique" is used to generate equations for the mechanical properties of each cell that result from its complex microstructure. These equations represent a new material for which the aggregate properties evolve as the microstructure changes with the application of strain. The micromechanical model can run in parallel with the main Finite Element Analysis (FEA) code, generating what is essentially a new stiffness matrix for the material at each time step. This approach enables a complex fibrous material to be represented by relatively few elements, thus improving computational performance without loss of mechanical fidelity.

To validate this model and to explore its utility in simulating the complex micromechanical behavior of biological tissues, we have again turned to heart valve tissue as the object of interest.

[5] Freed A.D., Einstein D.R., Vesely I., Invariant formulation for dispersed transverse isotropy in aortic heart valves: An efficient means for modeling fiber splay. Biomechanics and Modeling in Mechanobiology, 4:100-117, 2005.

We have shown before that the modulus of mitral valve chordae varies with chordal type. Even though the total amount of collagen is the same for all three types, the fibril size distribution is different (Fig. 4A,B). In a preliminary study to test the predictive ability of a micromechanical analysis, we simulated both the effects of collagen crimp and collagen fibril diameter. Collagen crimp is expected to affect the ultimate extensibility of these tissues and collagen fibril distribution is expected to affect the tangent modulus, as predicted by our structural model. Although these two phenomena occur at different scales, for the sake of simplicity, we generated structural models that incorporated both at once. The collagen crimp was set to 16.8, 12.6 and 10.8 mm for basal, marginal and strut chordae (Fig. 4C). The collagen fibril size distribution was composed of various ratios of thick and thin fibers of diameter 2, 4 and 6. Different combinations of these fibers were placed in the simulation grid (Fig. 4C), to mimic the fibril size distribution shown in Fig. 4B, albeit at a much coarser resolution. In each case, the volume fraction of fiber and matrix was kept at 50%, so that any mechanical differences resulted only from the differing microstructure. Starting values for collagen fibril stiffness were inferred from force spectroscopy data while matrix properties were estimated from pre-transition stress-strain data. The model was loaded incrementally and an effective stress/strain curve for the "material" was generated. Interestingly, this very simple model demonstrated the same pattern of increasing extensibility and decreasing tangent modulus in the order marginal, basal, strut (Fig. 4D), exactly as was measured experimentally. Probing deeper into the stress environment between the fibrils (Fig. 4E) reveals the reason why chordae with a lower crimp period (more crimped collagen) and larger diameter collagen fibrils have a lower tangent modulus. The larger fibrils bear a greater proportion of the stress than the thinner fibrils at a lower extensions – essentially when they are still more crimped and thus softer. This kind of insight would have been difficult to obtain without access to micromechanical models.

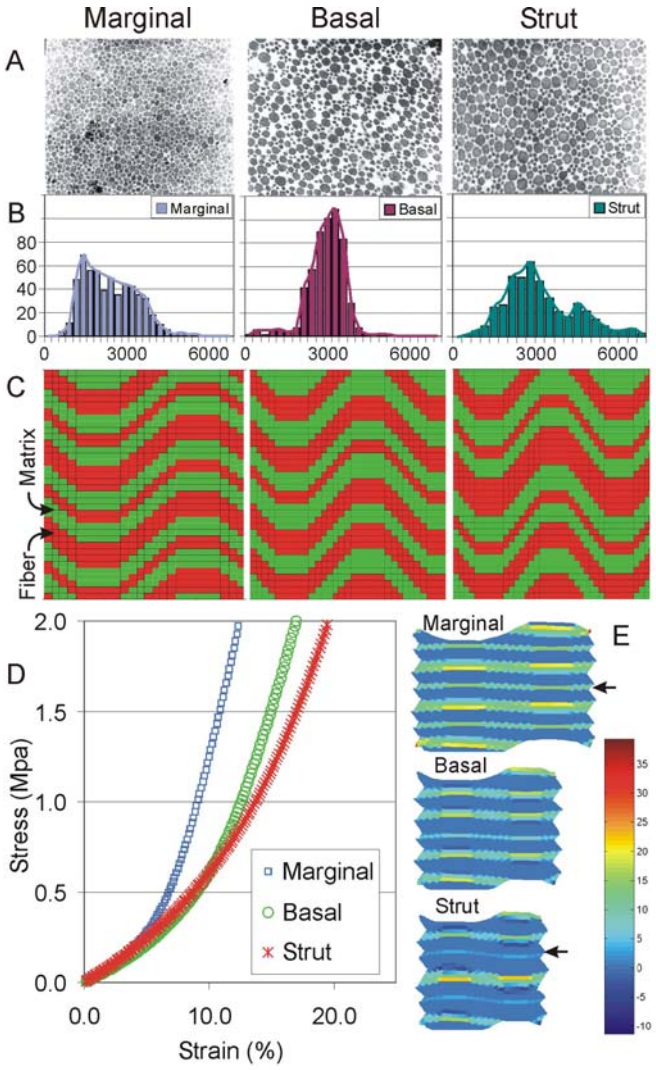

Figure 4: (A) Electron microscopy images of collagen fibrils in marginal, basal and strut chordae and their corresponding fibril diameter distributions (B). (C) The corresponding micromechanics model of each chordae. (D)The model demonstrated the same reduction in stiffness in the order of marginal, basal, and strut, as did the original mechanical data. (E) The distribution of the internal stresses, at a total stress of 2MPa, shows that the thin fibrils (arrows) in the strut chordae are stressed less than the thin fibrils in the marginal chordae, pointing to possible mechanism for the stiffness variation.

(f) Implementation of inverse methods

The advantage of a constitutive model is speed, at the expense of fidelity. The advantage of a micromechanics approach is fidelity, possibly at the expense of speed. To obtain the best of both approaches, we have considered hybrid approaches. A hybrid approach between constitutive and microstructural modeling is regional tuning of material properties using inverse methods. Connective tissues, such as heart valves and blood vessels, have spatially varying material properties. However, a small set of constitutive models can be used for the entire structure if their constants are tuned so that the mechanics of the individual finite elements represent the mechanics of tissue at the same location. In preparation for this project, we have developed an inverse method based on the response surface methodology (RSM) that can be coupled to whole tissue loading experiments[6].

Like all inverse FEA methods, RSM is driven by a series of forward FEA simulations that generate synthetic data whose deviation from the real experimental data needs to be minimized. The solution space has as many dimensions as there are parameters to be tuned, and the response surface usually contains many local minima. The response surface methodology first constructs a low order approximation to the response from a small number of forward simulations distributed through the solution space. The minimum of one response surface becomes the starting point for the next set of simulations. The parameter space is contracted with each iteration so that, in the neighborhood of the global minimum, finer features of the response are captured. This cycle of forward solutions followed by the minimization of the objective function is repeated until some minimal residual is reached. The approximate nature of the response surface over a wider parameter space at the beginning makes it relatively insensitive to local minima and experimental noise. Because minimization proceeds along the approximate response surface, RSM is an inherently parallel method, and thus is well-suited to massively parallel computer architectures. The actual tuning can be done on data sets from isolated tissues, whole vessel loading experiments or 3-D image data from patients. Indeed, in the experiment shown in Fig. 5, we see that a simulation of vessel clamping (one of the objectives of this project), shows a pattern of curvature in the clamped zone that is very similar to the curvature of the real tissue being clamped (in this case a pig aorta). Where inverse methods are particularly useful is the blending of experimental data from many sources into a single material model. For example, the pressurization experiments shown in Fig. 2 can be used as target data along with the experimental data

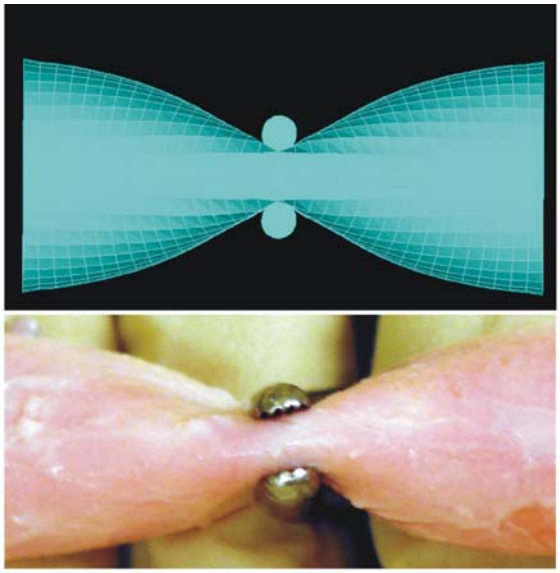

Figure 5: Image (bottom) of a presurized segment of pig aorta being clamped with forceps, simulating one of the key features of virtual surgery training - manipulating tissues. The image at the top is an FEA simulation of the same condition, complete with fluid/solid interactions. By matching the deformed profiles of the FEA simulation to real experimental data of the same deformation, confidence can be had that the model matches reality. Tuning of such models can be done best through the inverse FEA methods.

[6] Einstein D.R., Freed A.D., Stander N., Fata B., Vesely I., Inverse Parameter Fitting of Biological Tissues: A response surface approach. Ann.Biomed.Eng., 33(12):1819-1830, 2005.

of Fig. 5, to arrive at a material model that can satisfy both conditions.

Key Research Accomplishments

Computational modeling of soft biological tissues is extremely challenging. Unlike conventional materials, where the stress/strain response is well characterized, biological materials are poorly understood. In the absence of a good experimental knowledge of tissue mechanics, formulation of constitutive models becomes even more challenging. Coupled with this lack of knowledge over detailed mechanics is a poor understanding of microstructure. Without an understanding of microstructure, complexity cannot be build into the models to improve predictive fidelity. Progress in this field has therefore come about by an iterative improvement in both modeling capability and an understanding of tissue structure and mechanics. We have become the leaders in this field, largely because of the support form the US Army. Over the 3 years of support (which has been extended due to the disruption of activities by the move from Ohio to California), we have developed the following key pieces of technology:

(i) A one-dimensional model of fractional order viscoelasticity that is representative of the hierarchical nature of complex biological tissues. This is the first-of-its-kind implementation of fractional order calculus in the analysis of biomaterials.

(ii) A micromechanical approach to modeling soft biological tissues that incorporates material and geometrical non-linearity. This is also a first-of-its-kind application of GMC to biological materials.

(iii) A computationally expedient and very accurate constitutive representation of the dispersed isotropy that is typical of biological tissues. This method is faster than other methods currently being used.

These three key pieces of technology form the foundation with which to study soft tissue behavior in more detail into the future.

Reportable Outcomes

The reportable outcomes of this research are the publications listed in the Footnotes of this report. These publications are summarized in the References section below. We believe that we have satisfied the main objectives of this research program – to generate a collection of novel, more accurate computational models and to validate them using a series of materials tests, including a vascular clamping experiement.

Conclusions

These models, however, are not yet ready for implementation into surgical simulators. They are still much too slow for real time use. We expect that in the future, we and others will take these models and implement them in faster hardware and software, and also simplify them so that the essence of the features of soft tissues that are necessary for their use in surgical simulation, can be finally implemented in real training systems.

References

[1] Doehring T.C., Carew E.O., Vesely I. The effect of strain rate on the viscoelastic response of aortic valve tissue: a direct-fit approach. Ann.Biomed.Eng. 32(2):223-32, 2004.

[2] Doehring T.C., Freed A.H., Carew E.O., Vesely I., Fractional order viscoelasticity of the aortic valve: An alternative to QLV. J. Biomech. Eng. 127(4):700-8, 2005.

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[5] Freed A.D., Einstein D.R., Vesely I., Invariant formulation for dispersed transverse isotropy in aortic heart valves: An efficient means for modeling fiber splay. Biomechanics and Modeling in Mechanobiology, 4:100-117, 2005.

[6] Einstein D.R., Freed A.D., Stander N., Fata B., Vesely I., Inverse Parameter Fitting of Biological Tissues: A response surface approach. Ann.Biomed.Eng., 33(12):1819-1830, 2005.